IN THE CLAIMS:

Please amend claims 20, 22 and 29 as follows:

1-19. (Cancelled)

20. (Currently Amended) An egg-laying chicken whose somatic ~~lymphoid~~ cells contain an expression system comprising (i) a first DNA sequence encoding a human gamma isotype immunglobulin constant region having a CH2-CH3 region in an Fc domain of the constant region; (ii) a second DNA sequence encoding a human immunoglobulin variable region; (iii) a third DNA sequence comprising an immunoglobulin-gene derived promoter sufficient for expression of the human immunoglobulin constant region in the chicken; wherein the egg-laying chicken produces eggs whose yolk contains human gamma isotype immunoglobulin having a constant region encoded by the first DNA sequence and a variable region encoded by the second DNA sequence ~~and wherein the constant region has an undisrupted CH2-CH3 interface~~.

21. (Cancelled)

22. (Previously Presented) A method of producing a human immunoglobulin protein in an egg of an egg-laying -chicken comprising:

constructing a vector comprising an expression system comprising: (i) a first DNA sequence encoding a human gamma isotype immunoglobulin constant region having a CH2-CH3 region in an Fc domain of the constant region (ii) a second DNA sequence encoding a human immunoglobulin variable region, and (iii) a third DNA sequence comprising an immunoglobulin-gene derived promoter sufficient for expression of the human immunoglobulin constant region in the chicken, and

incorporating the vector into a pluripotent chicken cell line,

injecting the cell line into a chicken embryo, hatching an egg-laying chicken that produces an egg whose yolk contains human gamma isotype immunoglobulin having a constant region encoded by the first DNA sequence and a variable region encoded by the second DNA sequence ~~and wherein the constant region has an undisrupted CH2-CH3 interface~~.

23. (Previously Presented) A method according to claim 22 wherein the vector is further comprised of a negative selection marker.

24. (Previously Presented) A method according to claim 23 further comprising the step of isolating the human immunoglobulin from the egg.

25. (Previously Presented) A method according to claim 24 further comprising the step of conjugating the immunoglobulin to a toxin.

26. (Previously Presented) A method according to claim 24 further comprising the step of formulating the human immunoglobulin in a pharmaceutical formulation.

27. (Cancelled)

28. (Cancelled)

29. (Currently Amended) The chicken of claim 20 wherein the egg contains at least 3.46 ~~345~~ ng of human gamma isotype immunoglobulin per ml of egg yolk.

30. (Previously Presented) The chicken of claim 20 wherein the expression system is further comprised of an enhancer.

31. (Previously Presented) The chicken of claim 20 wherein the second DNA sequence encodes a human immunoglobulin variable region that is specific for an antigen.

32. (Previously Presented) The chicken of claim 31 wherein the antigen is a pathogen.

RESPONSE

Inventorship

Applicants note the named inventors and currently believe that the inventorship is correct as stated.

Oath/Declaration

Substitute declarations are submitted to state the correct claim for priority.

Priority

The instant application is amended to specifically refer to the prior application under 37 CFR 1.78(a)(2) and (a)(5).

Drawings

A replacement Figure 4 is submitted.

Claim 31 Objection:

Applicant submits that claim 31 is proper and further limits claim 20 because it distinguishes variable region sequences that code for an antibody that is specific for an antigen verses those that are not and may not reflect affinity maturation. Numerous examples exist of antibodies having variable regions that are not specific for an antigen. For these reasons, Applicants submit that the rejection is traversed.

The regulatory regions (promoters, enhancers, etc.) derived from an immunoglobulin gene are disclosed at pages 2, 3, 7, 8, 9, 11, and 15. Specifically as to the Ig-derived promoter, this feature is also described in the Morrison et al. paper (PNAS 1994) referred to at page 7 (PCT version of the specification) which is specifically incorporated by reference in the application.

35 USC § 112, 2nd paragraph

The claims are amended to render moot the Examiner's objections to the terms "somatic lymphoid cells" and "CH2-CH3 interface" and to correct the typographical error of "345" ng/ml yolk.

With respect to the written description of the regulatory region claimed, the specification discloses both that the promoter is derived from an immunoglobulin gene and that a cell-specific promoter is preferred. At column 12, lines 7-10, the specification states:

> Features that limit expression to particular cell types can also be included. Such features include, for example, promoter and regulatory elements that are specific for the desired cell type.

In particular, the application, at page 7, line 23, refers to the preparation of chimeric antibodies according to the procedure of Morrison, et. al., wherein low levels of expression were detected and the issue of operability of the promoter was considered. The "immunoglobulin gene-derived promoter" described in the specification is shown by the Morrison et al. article to be completely conventional in the art.

The relevant, structural characteristics described by the specification are precisely that encompassed by the claim, namely a promoter that meets the present limitation of the claim in an "immunoglobulin gene-derived promoter" that is "sufficient for expression of the human immunoglobulin constant region in a chicken." Promoters are typically described by the gene that they regulate and the effect on expression that they achieve. Accordingly, the description of the specification provides the only relevant identifying structural characteristics that identify to one of ordinary skill that the Applicants were in possession of what is now claimed.

Moreover, it should be noted that the Morrison et al. article was published in 1984, and by the time of the filing of the present specification, the use of promoters to drive the expression of a xenogenic immunoglobulin gene was well known to one of ordinary skill in the art, and that differences between the two species were demonstrated not to impact expression of immunoglobulin gene derived promoters. To demonstrate this point, applicants have provided a series of references to show that various immunoglobulin-derived promoters have been used to drive expression of the chicken immunoglobulin coding sequences and vise versa. For example, chimeric mouse-human coding regions for light and heavy chains directed against a DNS antigen have been prepared using a murine immunoglobulin 5 prime promoter region (L.K. Tan et al., "Influence of the hinge region on complement activation, C1q binding and segmental flexibility in chimeric human immunoglobulins," Proceedings of the Nat'l Acad. of Sciences 87:162-166, 1990; P.D. Chuang et al., "Elimination of N-linked glycosylation sites from the human IgA1 constant region: effects on structure and function," J. of Immun. 158:724-740, 1997). These genes have been expressed in chicken B-cells as well (see S.M. Mohammed, et al., "Deposition of genetically engineered human antibodies into the egg yolk of hens," Immunotechnology 4:115-125, 2000). Moreover, a fragment of chicken genomic DNA that includes Vλ, Jλ and Cλ coding exons and 1.4 kb of 5' prime regulatory sequence and 4.8 kb of 3' coding sequence was transfected into the mouse genome. Rearrangement of the transgene was observed in each of three transgenic mouse strains. (D. Bucchini et al., "Rearrangement of a chicken immunoglobulin gene occurs in the lymphoid lineage of transgenic mice," Nature 326:409-410, 1987).

Still further, in mice, human immunoglobulin regulatory sequences have been employed numerous times to express human antibodies and coded by human DNA sequences in murine B-cells

(L.D. Taylor et al., "Human immunoglobulin transgenes undergo rearrangement, somatic mutation and class switching in mice that lack endogenous IgM," Int'l Immun. 6:579-591, 1993; Lonberg, et al., Antigen-specific human antibodies from mice comprising four distinct genetic modifications; Nature 368, 856-859 (1994); D.M. Fishwild, "High-avidity human IgGκ monoclonal antibodies from a novel strain of minilocus transgenic mice," Nature Biotech. 14:845-851, 1996).

Accordingly, at the time the invention was filed, it was well recognized by one of ordinary skill in the art that chicken and human immunoglobulin-derived promoters functioned in mouse B-cells and that murine immunoglobulin promoters functioned in chicken B-cells. Because of the interrelationship between human, mouse and chicken coding sequences and regulatory regions, one of ordinary skill in the art would recognize that the reference and instruction of the present specification to use an Ig-derived promoter and the instruction for cell-specific expression to readily select a promoter that would function to drive expression of an immunoglobulin heavy chain gene in a chicken was in fact a description of the critical structural features of the invention. Accordingly, the present specification provides a written description that reasonably conveys to one of ordinary skill in the art that the claimed invention was in possession of the applicants and the pending claims withstand scrutiny under Section 112, first paragraph.

The Examiner's citation to Lilly is readily distinguished from the present case. The specification in Lilly merely recited "vertebrate insulin cDNA" to support a claim to insulin cDNA itself. In contrast here, the claim is to an egg-laying chicken and related method where an immunoglobulin gene-derived promoter is adequately described in the specification as the promoter taken from an immunoglobulin gene and that drives expression – there is no more specific structural

definition that can be made because the derivation of the promoter gene is the structural definition of the promoter. The gene from which it is derived is the structural definition of the sequence.

Subsequent to Lilly, the Federal Circuit clarified the written description requirement of § 112 in Enzo Biochem Inc. v. Gen-Probe, Inc., 323 F.3d 956, (Fed. Cir. 2002). There, as in the present case, the claim did not address a sequence itself, but encompassed hybridization probes.

In Enzo, the court properly stated the value of functional descriptions of genetic material, stating:

> "It is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement."

Referring specifically to the applicable PTO guidelines, the court held:

> "The written description requirement can be met ... by disclosure of sufficiently detailed, relevant identifying characteristics, i.e. ... functional characteristics when coupled with a known or disclosed correlation between function and structure..."

As the references provided above establish, a known correlation exists between promoters that express Ig genes across species and that the promoter is readily derived from an Ig gene. The specification describes the "detailed, relevant identifying characteristic" of the promoter claimed, namely an Ig-derived promoter, and couples that structural characteristic with a functional characteristic, namely that expression of human immunoglobulin constant region occurs in a chicken.

Applicants submit that the present claims are in condition for allowance and requests such action accordingly. If an interview would facilitate examination of this application, the Examiner is invited to contact the undersigned at 949/567-6700 X 7740.

The Commissioner is authorized to charge Orrick, Herrington & Sutcliffe's Deposit Account No. **150665** in the amount of **$475.00** for a one month extension fee and for any fees that may have been overlooked and to credit any overpayments to said Deposit Account No. **150665**.

Respectfully submitted,

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Dated: May 28, 2004

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